AF/1617

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	
Walter ELGER et al.	:	Group Art Unit: 1617
Serial No.: 09/744,574	:	Examiner: M. Bahar
Filed: 5 April 2001	:	

For: USE OF BIOGENIC ESTROGEN SULFAMATES FOR HORMONE REPLACEMENT THERAPY

do not enter the amendment MB

REPLY BRIEF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Further to the Examiner's Answer mailed on July 2, 2003, please consider the following remarks.

Remarks

The Double Patenting Rejection

Applicants contrary to the allegation of the Examiner do not acquiesce in the provisional double patenting rejection. The double patenting rejection was not addressed in the Brief on Appeal because applicants are not appealing said issue. The double patenting rejection is only a provisional rejection and it is premature to determine whether a terminal disclaimer is necessary to overcome the same as no allowable subject matter has been identified in at least the present application. Applicants plan to address this issue after allowable subject matter is identified. Furthermore, upon entry of the accompanying amendment, the double patenting rejection may be moot.

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as First Class Mail in an envelope addressed to: Commissioner of Patents, P O Box 1450, Alexandria, VA 22313-1450 on: 2 September 2003
Name: Isela Mestre
Signature:

The Prior Art Rejection

The Examiner has incorrectly interpreted the claims to mean that the specified dose should be multiplied by the number of days present between the interval specified. Based on the disclosure in the specification it is apparent to one of ordinary skill in the art that what is meant is that the specified dose is administered each day when administration takes place. Applicants point the Examiner's attention, for example, to Example 5, on page 18, specifying a one-time administration of 2 mg over 600 hours, i.e., 25 days. If the 2 mg dose is multiplied by the number of days, the amount would be 50 mg on day 25, which far exceeds the specified dose of 2.0-20 mg for intervals of 20 to 40 days. Thus, interpreting the claim to mean that the specified dose is to be multiplied by the number of days between the interval would effectively exclude at least example 5 from the claimed subject matter. One of ordinary skill in the art would thus interpret this claim to require the administration of the specified dose on each day of administration.

Applicants concurrently with this Reply Brief submit amendments to further clarify the intended meaning of the claims. However, even if the amendments are not entered, the meaning of the claims should be interpreted to mean that the specified dose is administered on each administration day, and not that the amount should be multiplied by the number of days within the interval. One of ordinary skill in the art would interpret the claims as proposed by applicants based on the disclosure in the specification, and thus, the claims should be interpreted in that manner.

Additionally, to simplify the issues, applicants cancelled some of the claims and rewrote some dependent claims in independent form in the concurrently filed amendment. However, even if the amendment is not entered, the arguments remain relevant to the full scope of the claimed subject matter. For convenience, applicants attach an appendix listing the claims assuming that the concurrently filed amendments to the claims are entered.

The Examiner alleges that there is no distinction between continuous administration and intermittent administration because the results in the simulated figure show that after the 4^{th} or 5^{th} administration, the same release profile is achieved as with continuous administration. This is because the objective is to achieve a release profile suitable for hormone replacement therapy with both administration modes. Thus, comparable results on release profile are only indicative

on this could only have expected a the same result in a human, and certainly could not have been motivated to use sulfamates intermittently. What would be the basis?

That is why applicants state in the specification that "it was found, surprisingly enough, that the release of the ... hormones in humans from the sulfamate prodrug proceeds much more slowly than in rats." (emphasis added) See page 11, last 3 lines on page. This is not a claim to unexpected result; but rather is a statement of no motivation for the invention.

Subinterrogatorily, in contrast to the results with a rat, the examples of the application demonstrate that elevated hormone levels remain in the blood for longer periods after a single administration. This result could not be expected from teachings or suggestions in the prior art. As to the allegation that the rat is not a good model, applicants note that such a conclusion or allegation could not be made until the applicants taught in the present specification that the results differ when the estradiol sulfamate is administered to a human. No basis for that conclusion exists in the prior art. One of ordinary skill in the art would have relied on the rat data as guidance for administration modes in the absence of any teaching in the prior art that would have taught otherwise.

The Examiner also alleges that the unexpected results discussed are not commensurate in scope with the claims. This is irrelevant for reasons discussed above; nevertheless, applicants respectfully disagree. While each example of the specification demonstrates a single administration, the results clearly demonstrate the unexpectedly elevated levels of hormones in the blood for an extended time, i.e., 48 hours (example 1), 1 week (example 3), 25 days (example 5), even after a single dose. These results establish that a subsequent dose after such time period will not be preceded by a zero level. This shows intermittent doses are effective.

These results are unexpected in view of the results achieved with the rat where the hormone levels were close to zero after 24 hours post administration. The specification additionally teaches that pharmacologically relevant blood levels were measured even after 4 weeks after a one-time administration. See specification on page 11, last 10 lines, and page 12, lines 1-5. Thus, the requirement to administer a second dose unit to replenish the hormone levels in the blood is not required the next day, but rather at a later time after the level of hormones decreases below acceptable levels. These results thus clearly demonstrate the need for only intermittent administration of the sulfamate prodrug of the estrogens to achieve the required levels of estrogens in the blood.

Based on these results, applicants found that, due to the slow release of the natural

estrogens, in connection with a high oral bioavailability of the steroid portion of the administered estradiol sulfamate, administration can be conducted at larger intervals, i.e., can be conducted intermittently. No teaching or suggestion in the prior art references to this effect can be found, which would supply the requisite motivation to one of skill in the art to administer the estrogen sulfamates intermittently. Thus, the intermittent administration of estrogen sulfamate is not obvious based on the references, and therefore the rejection should be reversed.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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Attorney Docket No.: GULDE-26

Date: September 2, 2003

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APPENDIX

THE CLAIMS

Claims 8-16 assume entry of the concurrently filed accompanying amendment.
Claim 17 assumes entry of the amendment accompanying the Brief on Appeal.

9. A method according to claim 11, wherein the estrogen sulfamate is estrone sulfamate, estradiol sulfamate, estriol sulfamate, N-acylsulfamate of estrone, estradiol or estriol having an acyl chain of up to 7 C atoms or mixtures thereof.

11. A method of achieving hormone replacement therapy in a woman comprising intermittently orally administering an estrogen sulfamate at a dosage of 0.5-5.0 mg on each day when administered in intervals of 5-10 days.

13. A method of achieving hormone replacement therapy in a woman comprising intermittently orally administering an estrogen sulfamate at a dosage of 2.0-20 mg on each day when administered in intervals of 20-40 days.

14. A method according to claim 11, further comprising the administration of a gestagen.

15. A method according to claim 14, wherein the at least one gestagen is levonorgestrel, desogestrel, norethisterone, medroxyprogesterone acetate, megestrol, cyproterone acetate, chlormadinone acetate, dienogest, drospirenone or a mixture thereof.

16. A method according to claim 14, wherein the at least one gestagen is continuously administered.

17. A method according to claim 16, wherein the continuous administration is in the form of an implant, in the form of an intrauterine release system or in the form of a combination thereof.

US 097445740HP1

Creation date: 07-14-2004
Indexing Officer: MBELAY - MESKEREM BELAY
Team: OIPEBackFileIndexing
Dossier: 09744574

Legal Date: 09-17-2003

No.	Doccode	Number of pages
1	CTMS	2

Total number of pages: 2

Remarks:

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